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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: **Viscomi G. C. et al.**

Confirmation No.: **7305**

Serial No.: **10/728,090**

Art Unit: **1624**

Filed: **December 5, 2003**

Examiner: **Kifle Bruck**

For: **Polymorph forms of rifaximin,
processes for their production
and use thereof in medicinal
preparations.**

Attorney Docket No.: **2965-128**

DECLARATION Under 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Giuseppe C. Viscomi, do declare and state as follows:

1. I am a citizen of Italy, born in Monterotondo (Rome) on January 18, 1954, residing at Via XXV Aprile n. 17, Sasso Marconi (BO) Italy.
2. I am a co-inventor of the invention described and claimed in the above-identified patent application ("the '090 application").
3. I received a degree in Industrial Chemistry from the University of Rome in 1978 (110/110). From 1978 to 1987 I was a researcher at Eniricerche in Monterotondo (Rome) and in Bioengineering Dept. Yale University (New Haven, CT, USA). From 1988 to 1992 I was head of Biotechnology DownStream Processing at Sclavo. From 1992 to 1998 I was Head of Immunological and Biotechnology Dept. at the company Alfa Wassermann S.p.A. in Bologna. Since 1998 I have been Research and Development Director at Alfa Wassermann S.p.A. in Bologna. I am the author of more than thirty scientific publications, most of which concern medicines and molecules with pharmacological activity. I am the inventor or co-inventor listed on more than twenty patents all concerning purification,

analysis and preparation of molecules with pharmacological activity. I am a member of the International Society for Interferon Cytokine Research and I was head of Scientific European Programs.

4. I have read and am familiar with the above-captioned '090 application and the September 16, 2005 non-final Office Action. I understand the Examiner has rejected claims 1-5 under 35 U.S.C. § 102, alleging that the specification is anticipated by Cannata V. et al. (US 4,557,866) and Marchi E. et al. (US 4,341,785).
5. Alfa Wassermann became aware of the existence of the polymorph forms of rifaximin (alpha, beta, gamma, delta and epsilon) some time before filing the priority application on November 7, 2003 (MI2003A002144).
6. Alfa Wassermann filed on March 3, 2005 a European priority application for the polymorph δ and ϵ and it will be extended in USA in 2006.
7. Rifaximin prepared according the old patents US '866 and US '785 was never tested for polymorph. Samples of batches manufactured in 2000-2001, presently re-tested, are composed either of mixture of polymorph (alpha and beta, and in some case alpha and epsilon) or different polymorphs.

Therefore it was possible at that time to obtain rifaximin polymorphs α and frequently also different polymorphs or mixture of them. Some example are reported below:

 - (i) A batch manufactured in 2001 and measured by X-ray diffractogram in 2002, turned out to be entirely composed of a polymorph subsequently defined "delta polymorph" (see Figure 1).
 - (ii) A batch manufactured in 2001, later analysed in 2002, consisted exclusively of the epsilon form (see Figure 2).
 - (iii) Another batch manufactured in 2001, instead, turned out to be a mixture of the alpha and epsilon form(see Figure 3).
 - (iv) A batch manufactured in 2004 (batch no. 2000 0827) and retested in 2005 was a mixture of the alpha and delta forms (see Figure 4).

8. Alfa Wassermann has moreover demonstrated by means of the following example, referring to batch no. 2000 0827 manufactured in 2000, that the crystalline forms are susceptible (before proceeding according to the present application) to transition from one form to another. A sample of this batch was stored in a small conventional screw-cap glass container; this sample was used to record the X-ray diffractograms after some time.

- (v) The diffractogram of June 2000 revealed that rifaximin belonged to the alpha form with a certain amount of the beta form (see Figure 5).
- (vi) The diffractogram of May 2001, on the other hand, turned out to be a mixture of the alpha and epsilon forms (see Figure 6).
- (vii) Finally, the diffractogram of February 2002 corresponded to a mixture of the epsilon and beta forms (see Figure 7).

In the meantime, the humidity content of the sample, due to repeated opening of the container and collection time of the samples under non-controlled humidity conditions had increased from the initial value of 1,3% to the final value of 4,5%, which was enough to change one form to another.

9. Alfa Wassermann has pointed out definite process in order to obtain pure polymorphs and not mixture of polymorphs using the information described in the US application 10/728,090 (2003) in order to obtain polymorph with definite pharmacological characteristics.

10. Alfa Wassermann observed a batch was constituted by a polymorph with peaks different from the polymorph described in the invention filed on November 7, 2003 and only after that time Alfa Wassermann was able to assign these peaks and find out the polymorph δ .

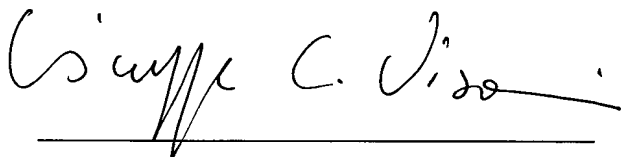
11. Alfa Wassermann, now with the knowledge of the polymorphs is able to reject production batch not complying with the polymorph requested. Only recently (from 2000 onwards) it has been gradually observed that the desired pure polymorph can be obtained only by optimising the various parameters of drying, e.g. temperature, time and other conditions.

- (viii) This has been confirmed by means of a test carried out recently. During the drying of batch no 050064 huge clots of product formed accidentally, preventing the rational drying of the polymorph, which

eventually turned out to be a mixture of the alpha and beta forms (see Figure 8). It was necessary to carry out again the crystallization and drying processes in order to obtain the pure polymorph.

12. I declare further that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: January 10, 2006

A handwritten signature in black ink, reading "Giuseppe C. Viscomi". The signature is written in a cursive style with a long horizontal line extending from the end of the name.

Giuseppe C. Viscomi

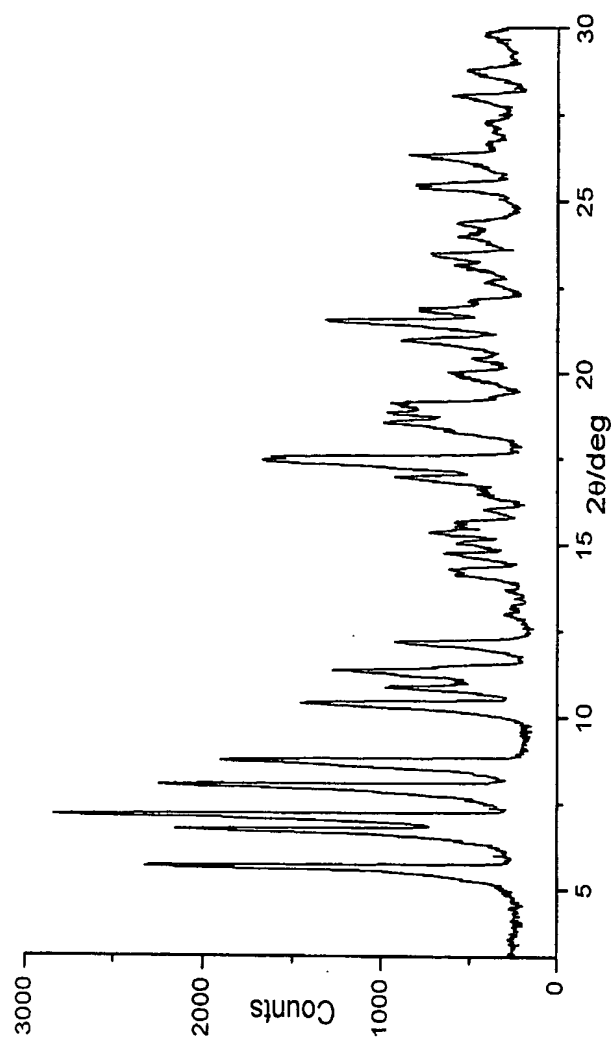


Figure 1 – Diffractogram of delta rifaximin

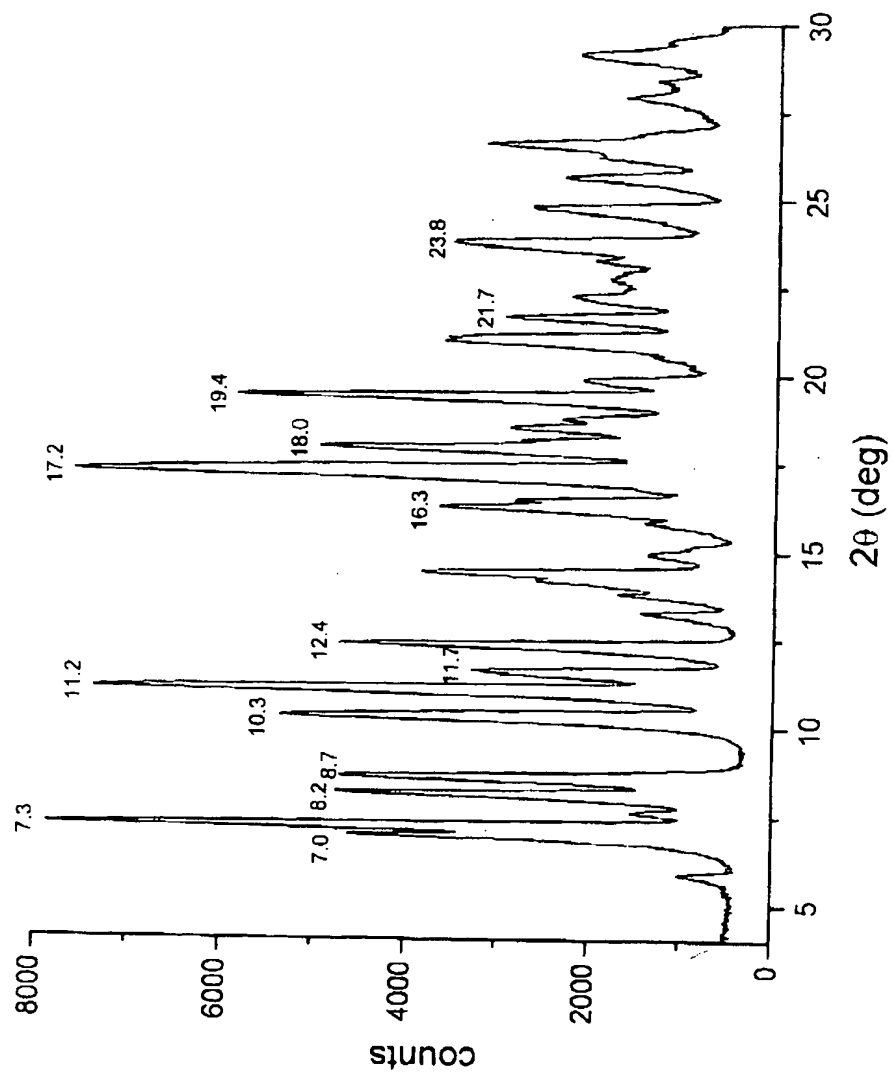


Figure 2 – Diffractogram of epsilon rifaximin manufactured in 2001

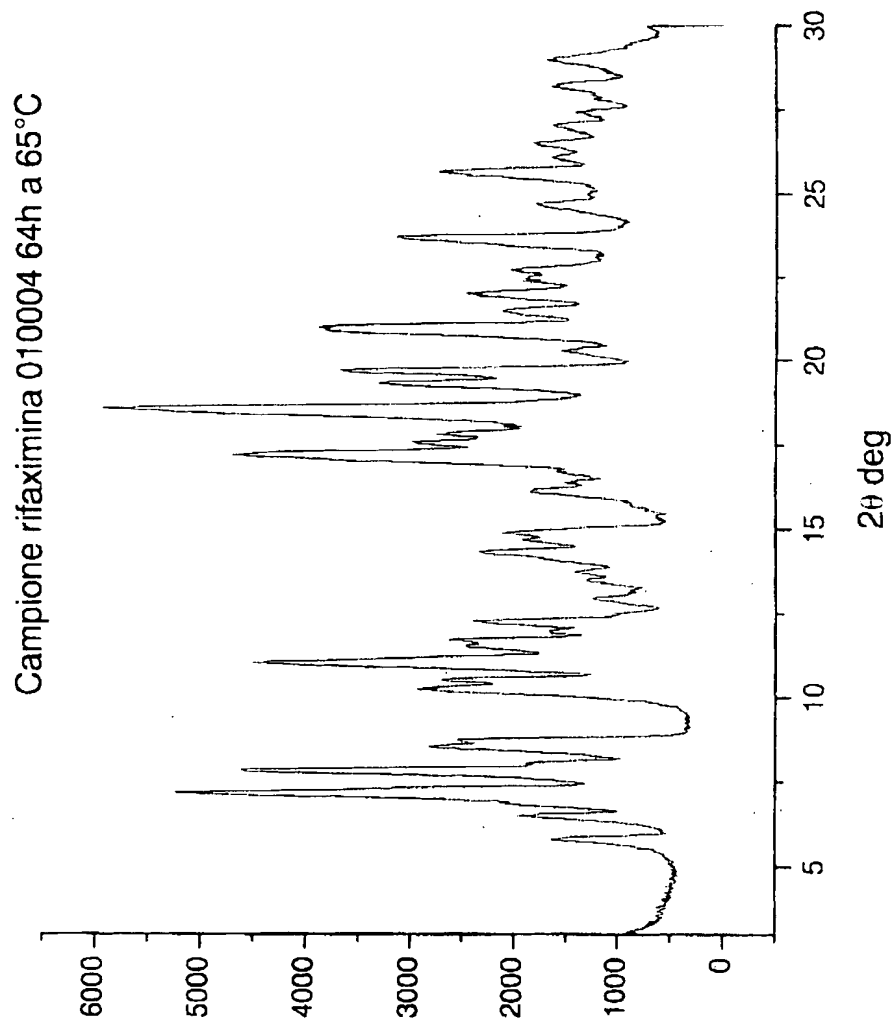


Figure 3 – Diffractogram of rifaximin – mixture of alpha and epsilon form manufactured in 2001

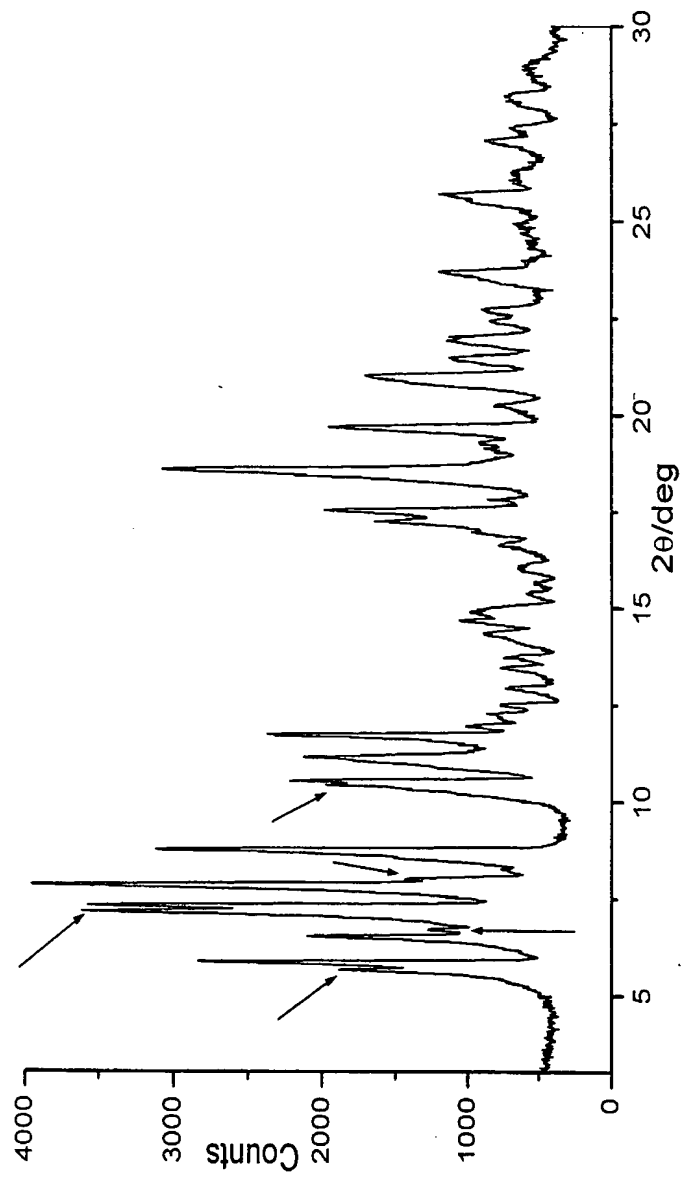


Figure 4 – Diffractogram of mixture of alpha and delta rifaximin (the arrows indicate the peaks attributable to the delta form)

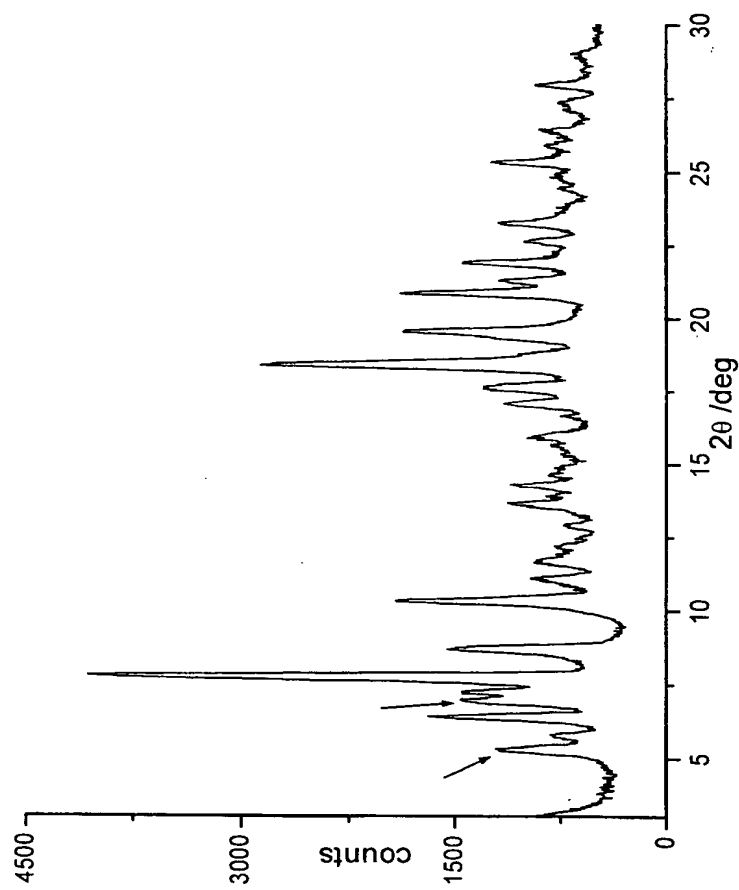


Figure 5 – Rifaximin batch No. 2000 0827: diffractogram of June 14, 2000 (the arrows indicate the peaks corresponding to the beta form only)

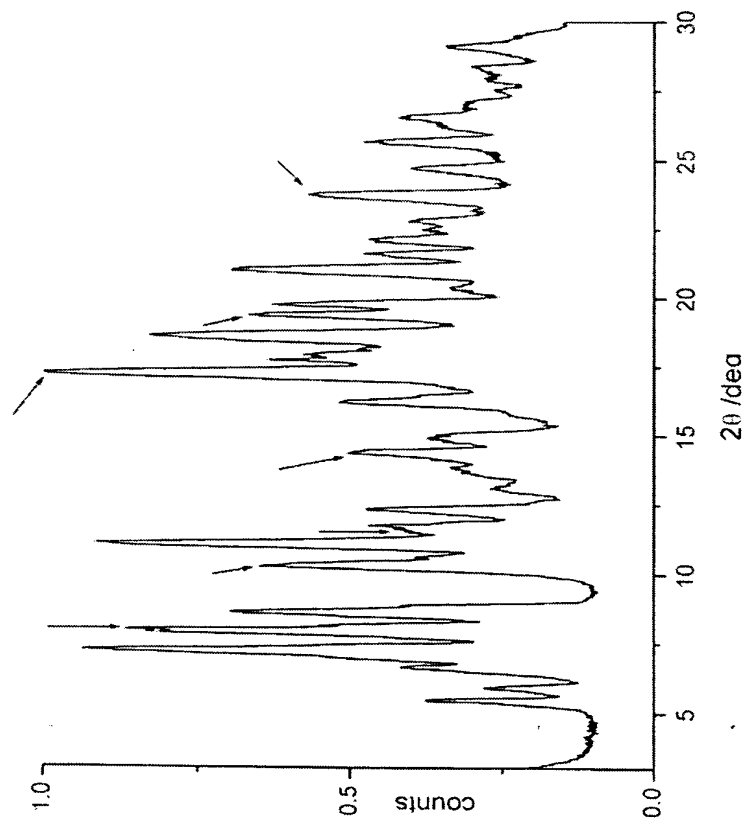


Figure 6 – Rifaximin batch No. 2000 0827: diffractogram of May 2001 (the arrows indicate the peaks corresponding to the epsilon form only)

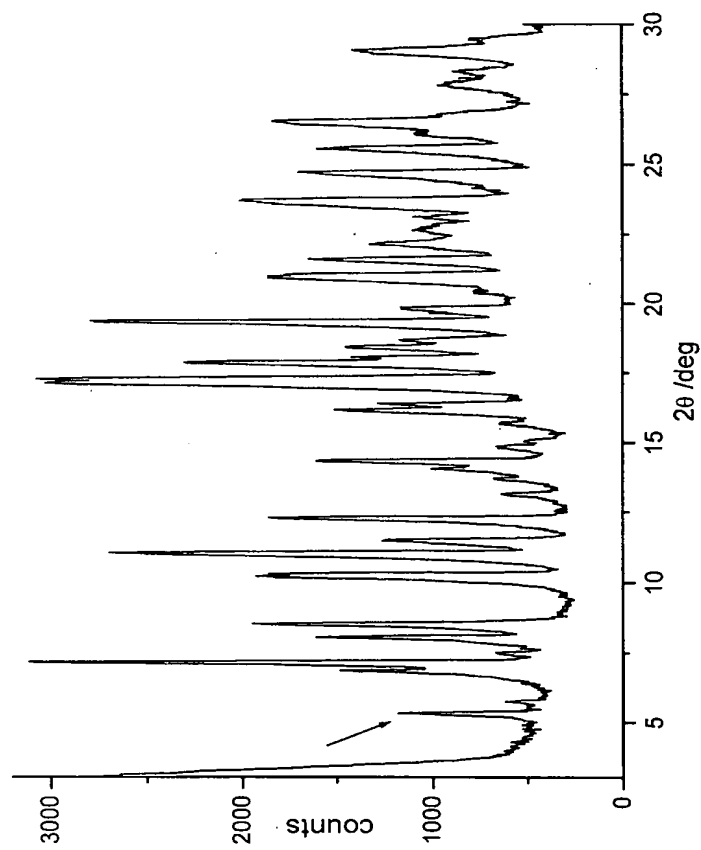


Figure 7 – Rifaximin batch No. 2000 0827: diffractogram of February 2002 (the arrows indicate the peaks corresponding to the beta form only)

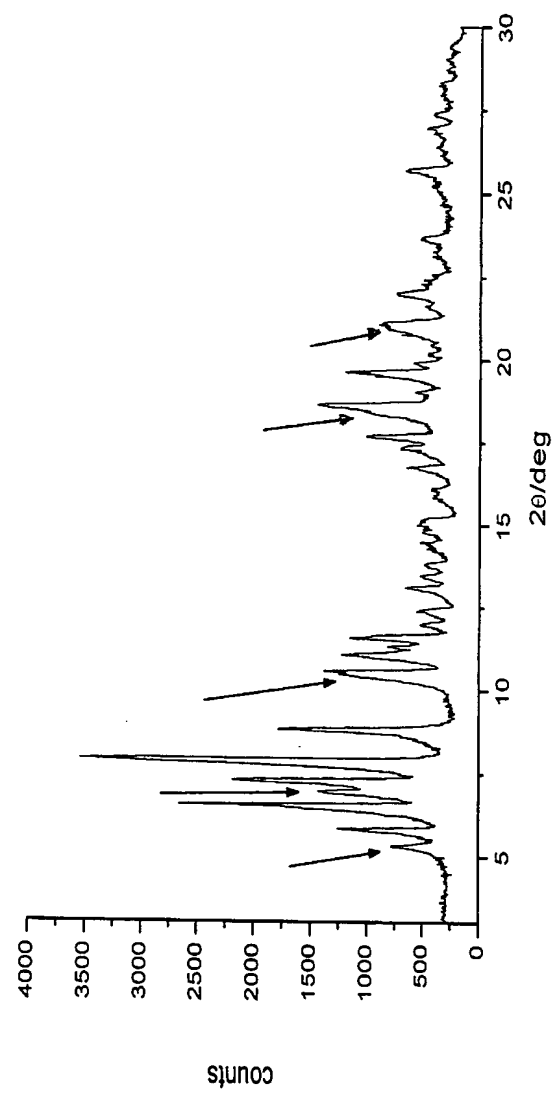


Figure 8-Diffractogram of mixture of alpha and beta rifaximin (the arrows indicate the peaks attributable to the beta form)